Foxc1 controls the growth of the murine frontal bone rudiment by direct regulation of a Bmp response threshold of Msx2.

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Public Summary:
The mammalian skull vault comprises paired frontal and parietal bones, which are formed by direct ossification of the calvarial mesenchyme. During this process, a group of signaling molecules and transcription factors play critical roles in controlling the cellular behavior of the mesenchymal cells in a spatial and temporal manner. Mutations in those genes cause defects in skull vault formation. In this study, we demonstrated the opposite roles of two transcription factors in initiating the osteogenic differentiation of the calvarial bones. One factor functions to repress the expression of the other factor by direct binding to its upstream enhancer, thus define the area of osteogenic differentiation of the mesenchymal cells.

Scientific Abstract:
The mammalian skull vault consists of several intricately patterned bones that grow in close coordination. The growth of these bones depends on the precise regulation of the migration and differentiation of osteogenic cells from undifferentiated precursor cells located above the eye. Here, we demonstrate a role for Foxc1 in modulating the influence of Bmp signaling on the expression of Msx2 and the specification of these cells. Inactivation of Foxc1 results in a dramatic reduction in skull vault growth and causes an expansion of Msx2 expression and Bmp signaling into the area occupied by undifferentiated precursor cells. Foxc1 interacts directly with a Bmp responsive element in an enhancer upstream of Msx2, and acts to reduce the occupancy of P-Smad1/5/8. We propose that Foxc1 sets a threshold for the Bmp-dependent activation of Msx2, thus controlling the differentiation of osteogenic precursor cells and the rate and pattern of calvarial bone development.

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